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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/332,866	06/15/1999	BEATRICE LEVEUGLE	AREX-PO1-008	3446

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	32

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/332,866	LEVEUGLE ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 June 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *05 June 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☒ The proposed amendment(s) will not be entered because:

(a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: *See Continuation Sheet*.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*.

Claim(s) objected to: *none*.

Claim(s) rejected: *14-15, 17, 20-21, 28-34 for reasons already of record.*.

Claim(s) withdrawn from consideration: *The amended claims 14-15, 17, 20-21, 28-34 and new claims 35-41, since they are not and will not be entered for reasons set forth above*.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Continuation of 2. NOTE: New claims 35 and 36 raises new issues for reciting "one member of an immunologic pair" and "an antibody fragment thereof". It is not clear what is"one member of an immunologic pair". Further "a fragment of an antibody" does not necessarily binds to the target antigen. New claim 39 raises a new issue for the use of the language "low dose" which is a relative term, and does not set forth the metes and bounds of the patent protection desired .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

It is noted that claims 14-15, 17, 20-21, 28-34 and new claims 35-41 are not and will not be entered and therefore are not examined.

The following are answers to Applicant's arguments concerning previous claims 14-15, 17, 20-21, 28-34.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

If claims 14-15, 17, 20-21, 28-34 were to be entered, claims 14-15, 17, 20-21, 28-34 remain rejected under 112, first paragraph, pertaining to lack of enablement of a method for inducing an immune response to prostate specific antigen, or an antibody that specifically binds to prostate specific antigen in a patient with prostate cancer, for reasons already of record in paper No:24.

Applicant argues as follows:

A) Example 12

Applicant argues that in paper No:12, the Examiner stated that this application is enabled for a method of treating prostate cancer, comprising administering antibody AR47.47 which specifically binds to the epitope of amino acids 139-163 of PSA (SEQ ID NO:1) (when claims were drawn to circulating PAS).

Applicant submits a Declaration by Dr. Schultes, stating that the animal model used in Example 12 is not representative of prostate cancer in human, wherein in

human prostate cancer, the disease progresses much more slowly timescale. Applicant asserts that thus the protocol of Example 12 is not designed to be predictive of the likehood of success or failure for treating human patients having prostate cancer.

Applicant further asserts that by the administration of the claimed AR47.47 (Ab1), antibody Ab3 equivalent to Ab1 could be expected to be produced via the idiotypic netwok, and antibody Ab3' which recognizes multiple epitopes of PSA could be produced via processing of an immune complex of AR47.47 and PSA.

Applicant argues that it is not relevant that PSA is a self antigen, because the instant application describes a method that breaks tolerance to self antigens. Applicant further argues that it would have been expected that adequate number of CTLs with high affinity for PSA would be produced.

Applicant further argues that if the claimed antibody AR47.47 could induce anti-idiotypic antibodies against PSA in a cancer free host, the claimed antibody would also be expected to induce anti-idiotypic antibodies against PSA in a host with prostate cancer. Applicant argues that the presence of PSA, produced by prostate cancer, is important for immune complex formation and induction of multiple epitopic anti-PSA antibodies (Ab3') and T cells specific for PSA.

Applicant recites the references by Chapman et al, Herlyn et al, stating that the technology of anti-idiotypic antibodies (Ab3) was well known at the time of filing of the instant application.

B) Example 11

Applicant argues that to prevent relapase, an immunotherapeutic approach using antibody AR47.47 would be very useful. Applicant argues that the mice in Example 11 were administered Ab1 (antibody AR47.47) prior to tumor inoculation to present an adequate model of early human prostate cancer, or human prostate cancer after primary treatment.

C) Experiments 8, 13, 10 and 14 in Example 12

Applicant argues that the Ab1 antibody did not induce a protective immune response in the majority of animals, as indicated by the fact that antibodies titers are not higher in AR47.47 treated mice than in the controls, is likely due to tumor implantation prior to immunization, and insufficient time to immunized the mice appropriately. Applicant argues that however, complete remission of 100 percent of animal models would not be required to expect that the subject treatment be useful in human patients. Applicant argues that the experimental data indicate that this treatment would be most useful in early stage of disease or as an adjunct treatment after first-line therapy, but would unlikely to be successful in late stage disease.

D) Ab2 correlation with method for inducing an immune response

Applicant argues that it was well known and accepted in the art that administration of Ab1 antibodies induce the formation of Ab2 antibodies, which ultimately induce the formation of Ab3 antibodies. Applicant further asserts that the claimed Ab1 AR47.47 also generates Ab3' antibodies which are induced by complexes of AR47.47 and the tumor antigen, PSA. Applicant asserts that the Ab3' response is a

subset of an anti-PSA response wherein the anti-PSA antibodies recognize epitopes distinct from the Ab1 antibody on a multi-epitope antigen such as PSA.

Applicant argues that induction of Ab2 and Ab3 antibodies is routine in the art, and is demonstrated in the specification. Applicant argues that in Example 10, a competitive binding assay demonstrate the presence of both Ab2 and Ab3 antibodies, as also indicated in the competitive assays of Example 7, 9, 11 and 12. Applicant asserts that Ab3 thus were successfully produced, and that one would expect that Ab3 would be produced as a consequence of the anti-idiotypic network.

E) Antibody induction specific for tumor.

Applicant argues that it was well known and accepted in the art that when Ab1 antibodies are administered in a patient, Ab3 are induced in sufficient amount in the host with tumor burden to elicit an effective immune response, as is set forth in the Schultes Declaration. Applicant further asserts that cancer patients produce PSA, which allows for immune complex formation between AR47.47 and PSA, and thus one would expect that a host with a pre-existing tumor burden would produce more anti-PSA antibodies than a host without tumor burden.

Applicant argues that Example 8 and Figures 10A-B clearly show that mice immunized with AR47.47 produce anti-PSA antibodies that bind to full length PSA and SEQ ID NO:1.

Applicant argues that the Examiner has not provided any factual evidence such as publications as to why the antibodies produced would not bind to SEQ ID NO:1 or circulating prostate specific antigen comprising SEQ ID NO:1. Applicant asserts that

thus the Examiner has not met the standards of enablement rejection as set forth in MPEP 2164.

The submission of the Schultes Declaration and the recitation of the references by Chapman et al, Herlyn et al are acknowledged, but have not been considered and entered, because Applicant has not presented good and sufficient reasons why the submitted Declaration, and references were not earlier submitted (see MPEP 37 CFR. 1.195).

Applicant's arguments in paper No: 30 have been considered but are found not to be persuasive for the following reasons:

Contrary to Applicant's assertion, the Examiner did not state that this application is enabled for a method of treating prostate cancer, comprising administering antibody AR47.47 which specifically binds to the epitope of amino acids 139-163 of PSA in paper No:12. It is noted that in paper No:12, the Examiner statement that this application is enabled for a method of treating prostate cancer, comprising administering antibody AR47.47 which specifically binds to the epitope of amino acids 139-163 of PSA is from a 112, first paragraph, scope rejection for enablement of a binding agent, wherein said statement is preceded by a requirement that Applicant could overcome the 112, first paragraph, enablement for being not enabled for a method of treating prostate cancer.

It is noted that Ab2 does not bind to PSA, it only binds to Ab1 or AR47.47, and mimics the structure of the antigen epitope or an idiotope of Ab1 that is distinct from the antigen binding site (specification, p.6). Thus detection of Ab2 does not mean that antibodies specific for PSA and anti-anti-idiotypic antibodies are detected.

It is further noted that contrary to Applicant assertion that the claimed invention describes a method that breaks tolerance to self antigen, no Ab3 antibodies, i.e. anti-anti-idiotypic antibodies which recognize the epitope of Ab1, AR47.47 comprising amino acids 139-163 of PSA (SEQ ID NO:1) have been identified in the specification. The assumed Ab3 antibodies are actually antibodies to PSA in mice free of tumor, and which do not have PSA as self antigen (Example 8). The specific epitopes of said assumed Ab3 antibodies are not known, and are called Ab3' antibodies by Applicant in the response, since the specification discloses that in the assay for Ab3 antibodies, the plate is coated with PSA (p.31), and there is no disclosure that the plate is coated with the amino acids 139-163 of PSA.

Concerning Example 11, Applicant argues limitation not in the claims, i.e. the limitation that a subject is pretreated with Ab1 antibody AR47.47 before development of prostate cancer.

Concerning Example 12, the Examiner agrees that it does not exactly represent a model of "treating" human prostate cancer, because the tumor is fast growing compared to mice lifespan. However, concerning a method for producing antibodies against PSA, whether antibodies are produced or not does not depend on the lifespan of mice because antibodies are known in the art to be routinely produced in mice. In Example 12, in all four experiments, 8, 13, 10 and 14, wherein **mice have cancers**, the amount of the putative Ab3 antibodies, which are actually antibodies binding to whole length PSA, and not anti-anti-idiotypic antibodies, are not different between mice treated with Ab1 antibody or AR47.47 and the control mice with tumor burden. Since there is no

difference between the control and the treated mice, one would not expect that the putative Ab3 antibodies that bind to the whole length PSA, is produced by Ab1 antibody or AR47.47, nor one would expect that any anti-anti-idiotypic antibody which recognizes the epitope of Ab1, AR47.47, or the amino acids 139-163 of PSA, would be produced by Ab1 antibody.

Further, although the art teaches that Ab3 or anti-anti-idiotypic antibody could be produced from Ab2, which in turn is produced by Ab1 for some antibodies, in some circumstances, Applicant has not shown that for any antibody, Ab1 could always or predictably produce Ab3, and as clearly shown in the specification, no Ab3 actually has been produced that could recognize the epitope of the Ab1 antibody AR47.47 in mice with or without tumor burden.

Concerning Applicant's arguments that cancer patients produce PSA, which allows for immune complex formation between AR47.47 and PSA, and that one would expect that a host with a pre-existing tumor burden would produce more anti-PSA antibodies than a host without tumor burden, it is noted that this argument is contrary to what has been well known in the art as T-cell anergy, wherein due to the overwhelming presence of antigen, the cytotoxic and proliferative response of tumor-specific T cells are blocked, as taught by Sherman et al and Smith et al, of record. Thus it is unpredictable that proliferative T cells that are needed for B cells activation and producing antibodies would not be anergic in prostate cancer patients. This is clearly shown by example 12 in the specification, wherein in mice with tumor burden antibodies

to PSA or the putative Ab3 are not different between the treated animals and the control.

Concerning Example 8 and Figures 10A-B, only mice without tumors are immunized with AR47.47 produce the putative Ab3 antibodies, which are actually anti-PSA antibodies that bind to full length PSA and SEQ ID NO:1. This example would not be applicable to a human patients because different from mice, human patients not only have PSA as self antigen, but also have tumor burden, both of these features would contribute to the suppression of production of anti-PSA antibodies in said patients, via self-tolerance and T cell anergy, as taught by Sherman et al, and Smith et al, of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

September 09, 2003

SUSAN UNGAR, PH.D
PRIMARY EXAMINER